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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,507	11/07/2001	Nick Wan	5047	3467

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EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,507	WAN ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) 1-5 and 12-17 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-17 are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-17 are pending.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, drawn to a method for the production of recombinant proteins in *Pichia pastoris*, classified in class 435, subclass 195.

II. Claims 6-11, drawn to a method for the production of recombinant glucocerebrosidase in *Pichia pastoris*, classified in class 435, subclass 200.

III. Claims 12-17, drawn to a method for the production of recombinant sphingomyelinase in *Pichia pastoris*, classified in class 435, subclass 197.

The inventions are distinct, each from the other because of the following reasons:

Inventions I-III are patentably distinct because they are directed to materially different methods for the production of different products such as recombinant proteins, glucocerebrosidase and sphingomyelinase. Methods of inventions I-III use different products such as DNAs encoding structurally and functionally different proteins/enzymes and have different utility.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their divergent subject matter, fall into different statutory classes of invention, and are separately classified and searched, restriction for examination purposes as indicated is proper.

Claims 1-5 are generic to a plurality of disclosed patentably distinct species comprising acid lipase, alpha glucosidase, alpha-L idronidase, alpha galactosidase, iduronate sulfatase, galactosamine-6-sulfatase, beta-galactosidase, and arylsulfatase B. If Group I were elected, Applicant would have been required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Jennifer Dupre on July 15, 2003 a provisional election was made with traverse to prosecute the invention of Group II, claims 6-11. Affirmation of this election must be made by applicant in replying to this

Office action. Claims 1-5 and 12-17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(l).

Priority

If applicant desires priority under 35 U.S.C. 119(e) based upon provisional application 60/248,806, a specific reference to said application must be made in the first sentence of the description or in an application data sheet. It should not state that the instant application is a "continuation" of provisional application 60/248,806 (see MPEP 201.11 IIIB).

Information Disclosure Statement

The instant application contains no IDS.

Specification

The disclosure is objected to because of the following:

On page 25, line 6, the specification recites "rh-GCR (Glucocerebrosidase)". Thus, it spells out only a part of the abbreviation. The examiner construed "rh-GCR" as "recombinant human glucocerebrosidase".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6-11 are directed to a method for the production of recombinant glucocerebrosidase or recombinant human glucocerebrosidase comprising culturing cells of *Pichia pastoris* which cells comprise a DNA molecule which encodes glucocerebrosidase (GCR). Therefore, the claims comprise the genus of DNAs encoding GCRs from any source and man made variants thereof as well as any allelic variant of human GCR.

As any chemical compound a DNA is described by its chemical structure. However, there is no description of the structure of any GCR or a DNA encoding thereof. Moreover, the specification fails to describe any other identifying characteristics or properties of DNAs encoding GCRs other than the functionality of encoding a GCR.

Furthermore, it is known that humans have various allelic variants of GCR genes (e.g., Beutler et al., 1992). Furthermore, there is no description of "high mannose carbohydrate structure" that is part of the requisite GCR molecule such as the number of carbohydrate chains and their carbohydrate composition. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite "high mannose structure". The specification does not define the number and composition of carbohydrate chains in said structure rendering the metes and bounds of the term unascertainable.

Claims 8 and 11 recite the limitation "wherein the cells are continuously cultured without the addition of molecular oxygen". This negative limitation defines the invention in terms of what it is not, rather than pointing out the invention rendering the metes and bounds of the claims unascertainable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. in view of Invitrogen Catalog (1998).

Friedman et al. (US Patent 5,549,892) teach that human GCR is needed for treatment of Gaucher's disease. They teach that it is an expensive form of therapy (column 1, lines 48-51). They teach the importance of GCR remodeling, i.e. its "high mannose structure" for the production of a pharmaceutically effective preparation. They

teach the production of a remodeled recombinant human GCR in mammalian (CHO) cells.

Invitrogen Catalog (1998) discloses the *Pichia pastoris* expression system and its "advantages over any other expression system" such as high expression levels, easy scale-up and inexpensive growth (page 19). It further discloses pGAPZα vectors comprising a constitutive GAP promoter designed to express proteins constitutively in *P. pastoris* without the need for methanol. Invitrogen catalog teaches the advantages of said vectors (page 22). Apparently, these vectors are used in the instant invention (specification, page 25, line 8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare recombinant human GCR with high mannose structure in *P. pastoris* cells using cells and vectors commercially available by Invitrogen. One of ordinary skill in the art at the time the invention was made would have been motivated to use *Pichia pastoris* expression system comprising pGAPZα vectors for the production of GCR in view of its therapeutic importance taught by Friedman et al. The advantages of *P. pastoris* system over expression in any other cells are taught by Invitrogen catalog. It would have been further obvious to use the continuous process in order to make the GCR production more effective and less expensive. pGAPZα vectors allow for continuous production of the desired recombinant protein because no addition

of methanol is required. Invitrogen catalog does not teach that the addition of molecular oxygen is needed for the protein expression in the *P. pastoris* system.

Conclusion

The art made of record and not relied upon is considered pertinent to applicant's disclosure.

Goodrick et al. (September 20, 2001) teach the production of human chitinase in a continuous constitutive *Pichia pastoris* expression system. This is the work by the current inventors describing the same system used for expression of chitinase (specification, pages 12-24).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

September 12, 2003